At a recent meeting of the Drug Utilization Review (DUR) Board at the Office of Vermont Health Access (OVHA), carvedilol (Coreg®) was recommended and approved for inclusion on the OVHA Preferred Drug List. As such, effective 5/1/2006, this agent will be available to prescribers without the need for prior authorization. In an effort to insure appropriate utilization of this agent, the following key clinical information is provided.

Background
Carvedilol is a nonselective, beta-adrenergic blocking agent that possesses additional alpha$_1$-adrenergic blocking activity and no intrinsic sympathomimetic action. Carvedilol was FDA-approved in the US in September of 1995.

Pharmacology/Indications
The combined alpha- and beta-blocking activity yields decreased cardiac output, decreased tachycardia, enhanced vasodilation and reduced peripheral vascular resistance.
Carvedilol is indicated for:

1) mild-to-severe (New York Heart Association [NYHA] Class II-IV) heart failure of ischemic or cardiomyopathic origin, usually in combination with other heart failure therapies (e.g., ACE Inhibitors, digitalis, diuretics)
2) left ventricular dysfunction (ejection fraction <= 40%) subsequent to an acute myocardial infarction, with or without clinically symptomatic heart failure
3) essential hypertension, either as monotherapy or in combo with other antihypertensive agents

Evidence – Heart Failure Treatment
Approximately 7,000 patients with mild-to-severe heart failure have been evaluated in placebo-controlled carvedilol trials. Several larger-scale outcomes-based trials have consistently demonstrated carvedilol's efficacy in prolonging life and reducing cardiovascular morbidity in the heart failure population. The following table provides results from some of the more significant evidence-based studies with carvedilol in heart failure patients:

Clinical Trial	Patients	Intervention	Follow-up	NYHA Class	Overall Mortality
US Carvedilol Trials[1,2]	LVEF ≤ 35% (n = 1094)	Carvedilol 25-50 mg po BID; placebo	Median 6.5 months	II, 52-53% III, 43-44% IV, 3%	Placebo, 7.8% Carvedilol, 3.2% *(p ≤ 0.01)*
Australia/New Zealand[3]	LVEF < 45% (n = 415)	Carvedilol 25 mg po BID; placebo	Mean 19 months	I, 29-30% II, 49-59% III, 11-21%	Placebo, 12.6% Carvedilol, 9.6% *(NS)*
Capricorn (2001)[4]	LVEF ≤ 40% Post-MI (n = 1959)	Carvedilol 25 mg po BID; placebo	Mean 1.3 years	Not Reported	Placebo, 15% Carvedilol, 12% *(p = 0.031)*
Copernicus (2003)[5,6]	Symptoms at rest or with minimal exertion (n = 2289)	Carvedilol 25 mg po BID; placebo	Mean 10.4 months	Not Reported	Placebo, 16.8% Carvedilol, 11.2% *(p = 0.0014)*
Comet (2003)[7]	LVEF ≤ 35% (n = 3029)	Carvedilol 25 mg po BID; Metoprolol tartrate 50 mg po BID	58 months	II, 48-49% III, 47-48% IV, 3-4%	Carvedilol, 35% Metoprolol Tartrate, 40% *(p = 0.002)*

Hypertension
While carvedilol has demonstrated positive results in reducing both systolic and diastolic blood pressure in patients with essential hypertension, and it does carry FDA-approved for this indication, this product is not recommended as a primary therapy for hypertension management. Carvedilol has not demonstrated superior outcomes to other much less-costly generic beta-blocker alternatives such as atenolol or metoprolol in hypertension management. Carvedilol requires twice-daily dosing versus numerous other once-daily anti-hypertensive treatment alternatives. Finally, carvedilol, because of its alpha-blocking effects, also carries a higher risk of orthostatic hypotension (including first-dose reactions), syncope, and dizziness versus alternative antihypertensive options, which may prove particularly problematic in a more aged population.

Place in Therapy
In light of this evidence, carvedilol's primary role today clearly lies with the management of patients with left ventricular systolic dysfunction and/or clinical heart failure. Current consensus guidelines clearly support the use of beta-blocker therapy, in combination with other therapies like ACE Inhibitors and diuretics, for all patients with these conditions. Carvedilol, along with bisoprolol and metoprolol succinate (Toprol-XL®), remain the beta-blockers with the most significant level of clinical evidence supporting positive outcomes in this population.

Important Dosing Information
In the treatment of patients with left ventricular dysfunction, it is critical that dosing be individualized, slowly titrated upward, and closely monitored by a physician during the up-titration phase. Prior to initiation of treatment, it is also recommended that patients be hemodynamically stable and that fluid retention be minimized.

Carvedilol is available as 3.125mg, 6.25mg, 12.5mg and 25mg tablets. The recommended starting dose of carvedilol is 3.125mg twice-daily for 2 weeks. Patients who tolerate a dose of 3.125 mg twice-daily may have their dose increased to 6.25, 12.5, and 25 mg twice-daily over successive intervals of at least 2 weeks. Patients should be maintained on lower doses if higher doses are not tolerated. A maximum dose of 50 mg twice daily has been administered to patients with mild-to-moderate heart failure weighing over 85 kg (187 lbs).

Patients should be advised that initiation of treatment and (to a lesser extent) dosage increases may be associated with transient symptoms of dizziness or lightheadedness (and rarely syncope) within the first hour after dosing. Thus during these periods they should avoid situations such as driving or hazardous tasks, where symptoms could result in injury. In light of potential vasodilatory symptoms with carvedilol use, but it may be useful to separate the time of dosing of carvedilol from that of a concomitant ACE inhibitor, or to reduce temporarily the dose of the ACE inhibitor.

Carvedilol should be taken with food to slow the rate of absorption. The dose of carvedilol should not be increased until symptoms of worsening heart failure or vasodilation have been stabilized. The dose of carvedilol should be reduced if patients experience bradycardia (heart rate <55 beats/minute). Episodes of dizziness or fluid retention during initiation of carvedilol can generally be managed without discontinuation of treatment and do not preclude subsequent successful titration of, or a favorable response to, carvedilol.

References:

1) *Circulation* 1996;94:2793-2816 2) *NEJM* 1996;334:1349-1355 3) *Lancet* 1997;349:375-380
4) *Lancet* 2001;357:1385-1390 5) *NEJM* 2001;344:1651-1658 6) *JAMA* 2003;289:712-718
7) *Lancet* 2003;362:7-13 8) GlaxoSmithKline. Package Insert for Coreg. June 2005